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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,407	08/01/2003	Douglas W. Losordo	58098 (71417)	6007

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EXAMINER	
O'HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,407	LOSORDO ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2005 and 16 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *4-7,10,14-16,20,22,23,28,29,35,43-65 and 69-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,9,11-13,17-19,21,24-27,30-34,36-42 and 66-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-74* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-74 are pending in the instant application.

Election/Restrictions

2. Applicant's election with traverse of Group I, Y27632, VEGF-1 and limb ischemia in the reply filed on January 30, 2006 is acknowledged. The traversal is on the ground(s) that the restriction requirements are improper, and that the subject matter of the groups represent different embodiments of a single inventive concept. Also argued is that a single, searchable, unifying aspect links all of the claims, that is modulating the activity of ezrin, a cytoskeletal protein. Also argued is that a sufficient search and examination with respect to the subject matter of all claims can be made without serious burden, and even if the groups of claims are drawn to distinct inventions, the Examiner must still examine the entire application on the merits because doing so will not result in a serious burden, which is especially true given the robust and extensive computerized search engines and databases at the Examiner's disposal.

This is not found persuasive because examining all of the claims would entail a serious burden. Although computerized search engines and databases help significantly in the search, the references in these databases are growing at a tremendous rate, and each claimed compound would require a separate search.

Applicant's election of Group I, claims 1-48 and 66-68 in the reply filed on May 16, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-7, 10, 14-16, 20, 22, 23, 28, 29, 35, 43-65 and 69-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-3, 8, 9, 11-13, 16-19, 21, 24-27, 30-34, 36-42 and 66-68 are currently under examination.

Information Disclosure Statement

3.1 Applicants are informed that Japanese publication 6 289679 is drawn to an image forming unit.

3.2 The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

4. The disclosure is objected to because of the following informalities.

4.1 In the legend to Fig. 1 on page 10, cyclin A is Fig. 1B and cyclin B is Fig. 1C, however in the figure cyclin A is 1C and cylcin B is 1B.

4.2 In the legend to Figure 13 on page 12, it is written that Figure 13C-D are photographs of mouse hindlimbs and Figure 13C is a graph, but Figure 13C is the photographs of mouse hindlimbs and Figure 13D is a graph.

4.3 37 C.F.R. §1.821(d) states:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

A sequence is disclosed in Table 1, pages 17-18, without the required reference to the sequence identifiers (SEQ ID NOS:). The instant specification needs to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. This can be resolved by adding a reference to the Table. For rules interpretation Applicant may call (571) 272-2510. See M.P.E.P. 2422.04.

Applicants are required to amend the specification and claims to comply with 37 C.F.R. §1.821(d).

4.4 The specification is also objected to because at page 45, lines 30-31, the reference to Figure 13 includes color, and the figure is in black and white.

Appropriate correction is required.

Claim Objections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 17-19, 21- 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5.1 Claims 17-19, 21- 27 are indefinite because claim 17 is drawn to a method of **inducing** formation of new blood vessels in a mammal, but it comprises decreaseing ezrin activity in an amount sufficient to **modulate** formation of the new blood vessels, which is different from inducing.

5.2 Claim 27 also recites the limitation "the method of claim **25,** wherein the angiogenic protein" There is no antecedent basis for this limitation in the claim, since it depends from claim 25.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 8, 9, 11-13, 17-19, 21, 24-27, 30-34, 36-42 and 66-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a method of inducing endothelial cell proliferation in a mammal or method of inducing formation of new blood vessels in a mammal

comprising administering decreasing ezrin activity by administration of Y27632, a specific RhoA kinase inhibitior (ROCK-2). ROCK-2 is induced by TNF to phosphorylate enzrin, a cytoskeletal protein which when phosphorylated is translocated to the nucleus and binds to the cyclin A promoter, inhibiting transcription and inhibiting cell proliferation. The specification teaches that TNF is expressed in arteries during atherosclerosis and restenosis with increased expression after balloon injury in multiple animal models, and that blocking TNF improves re-endotheliation after balloon angioplasty. The invention is drawn to abrogating the effects of TNF after vascular injury by administration of Y27632, or induction of new blood vessels. Example 14 shows that transplantation of dominant negative ezrin-transfected HUVECs improves blood flow recovery in nude mice hind-limb ischemia injury compared to HUVECs transfected with wild-type ezrin (Figure 13). *In vitro* experiments in the instant application demonstrate that in endothelial cells treated with TNF, enzrin was phosphorylated via ROCK-2, and the phosphorylated ezrin bound to the cyclin A promoter, and the phosphorylation of ezrin was completely inhibited by Y27632, and ezrin binding to cyclin A promoter was reduced (Example 15). Example 16 demonstrates that *in vitro*, treatment with Y27632 reversed ezrin/TNF mediated inhibition of endothelial cell proliferation in a dose dependent manner. Such results would indicate that Y27632 could be useful *in vivo* for treating ischemic vascular disease by enhancing endothelial cell. However, Shibata et al., Circulation, Vol. 103(2), 16 January 2001, pp. 284-289, demonstrate that administration of Y27632 has no effect on endothelial cell proliferation in a balloon injury in the rat carotid artery, which is the best-studied model of vascular remodeling after vascular injury (Shibata et al.). While Y27632 enhanced apoptosis of neoinitmal smooth muscle cells (Figs. 1-3, discussion), the authors found that

Y27632 had no significant effects on reendothelialization (Figure 4, discussion). Uchida et al., Biochem. Biophys. Res. Comm., Vol. 269, No. 2, pages 633-640 (2000), teach that Y27632, inhibits angiogenesis (page 635, first paragraph of discussion). HUVECs at 24 hours without Y27632 treatment showed capillarylike constructions (Fig. 1a), while treatment with Y27632 inhibited such constructions (Fig. 1c). Figures 2 and 3 also demonstrate that Y27632 could suppress angiogenesis in both *in vitro* (Fig. 2a-d, without Y27632, and Fig. 2e-h, with Y27632) and *in* vivo (Fig. 3d and e, mouse dorsal skin model with and without Y27632, respectively). Xue et al., Hepatology, October 2003, Vol. 38, No. 4, Suppl. 1, pp. 400A, demonstrates that tumor growth and intrahepatic metastases of mouse hepatocellular carcinoma (HCC) were mediated through Rho/ROCK signaling, and Y27632 suppressed intrahepatic metastases, mainly by anti-angiogenic mechanism, and also by its effect on hepatic stellate cells (HSCs, indirect). The effect of Y27632 was also tested on HUVECs. Y27632 inhibited HUVECs migration in a dose dependent manner and suppressed tube formation as well as proliferation.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

It is acknowledged that the level of skill of those in the art is high. However, the teachings of the art teach away from the claimed invention. There are no examples of in vivo

data in the specification, which provides only *in vitro* experimental data. Biological systems are complex, and while cells in an *in vitro* system may behave in a certain way, it is not necessarily predictive of *in vivo* activity. Thus, the specification fails to teach the skilled artisan how to use the Y27632 to induce endothelial cell proliferation, treat ischemia or induce angiogenesis in a mammal. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the polynucleotide for the above stated purposes.

Due to the large quantity of experimentation necessary to determine under what conditions Y27632 could be used for the claimed purposes, the lack of direction/guidance presented in the specification regarding *in vivo* applicability, lack of *in vivo* working examples and unpredictabity between in *vitro* and *in vivo* results, the teachings of the art which teach away from the invention and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

Conclusion

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER